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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/863,693	05/23/2001	W. Robert Arathoon	P1099R1C1	1782

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MERCHANT & GOULD PC
P.O. BOX 2903
MINNEAPOLIS, MN 55402-0903

EXAMINER
RAWLINGS, STEPHEN L

ART UNIT	PAPER NUMBER
1642	12

DATE MAILED: 03/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/863,693	ARATHOON ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,8,9,11,19,20 and 30-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,8,9,11,19,20 and 30-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The amendment filed January 7, 2003 in Paper No. 11 is acknowledged and has been entered. Claims 30-44 have been added.

2. Claims 1, 8, 9, 11, 19, 20, and 30-44 are pending in this application and are currently under prosecution.

Grounds of Claim Rejections Withdrawn

4. Unless specifically reiterated below, the grounds of objection and rejection set forth in the previous Office action mailed October 7, 2002 (Paper No. 8) have been withdrawn.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1, 8, 9, 11, 19, 20, 33-38, and 41-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mallender, et al (*Journal of Biological Chemistry* **269**: 199-206, 1994), as evidenced by Gulliver, et al (*Journal of Biological Chemistry* **269**: 7934-7940, 1994), in view of U.S. Patent Nos. 5,731,168-A, 5,807,706-A, and 5,821,333-A.

Mallender, et al teaches a method for preparing a bispecific antibody fragment comprising culturing a host cell comprising nucleic acid encoding a first polypeptide comprising a first binding domain and a second polypeptide comprising a second, different binding domain and recovering the bispecific antibody from the host cell culture. Both the first and second binding domains of the bispecific antibody comprise a heavy chain domain that interacts with a light chain. As evidenced by the teachings of

Gulliver, et al the variable light chains of the first and second polypeptides are nearly identical. Mallender, et al teaches that the construction of a model bivalent bispecific molecule provides a foundation for future assembly of similar molecules designed to identify parameters involved in enhanced binding of antibodies due to avidity and dual specificity.

However, Mallender, et al does not teach a method for preparing a bispecific antibody wherein the first polypeptide comprises a multimerization domain that interacts with a multimerization domain of the second polypeptide. Mallender, et al does not teach that the first and second polypeptides can comprise an antibody constant domain, namely an antibody constant domain from a C_H3 domain or an IgG. Mallender, et al does not teach that the multimerization domains of the first and second polypeptides comprise a free thiol positioned so that a disulfide bond is formed between the first and second polypeptides upon the interaction of the multimerization domains. Finally, Mallender, et al does not teach the host cell can be a mammalian cell.

U.S. Patent Nos. 5,731,168-A, 5,807,706-A, and 5,821,333-A teach a method for preparing a bispecific antibody comprising culturing a host cell comprising nucleic acid encoding a first polypeptide comprising a first binding domain and a second polypeptide comprising a second, different binding domain and recovering the bispecific antibody from the host cell culture. Both the first and second binding domains of the bispecific antibody comprise a heavy chain domain that interacts with a light chain. The first polypeptide comprises a multimerization domain that interacts with a multimerization domain of the second polypeptide. The first and second polypeptides comprise an antibody constant domain, namely an antibody constant domain from a C_H3 domain or an IgG. The multimerization domains of the first and second polypeptides comprise a free thiol positioned so that a disulfide bond is formed between the first and second polypeptides upon the interaction of the multimerization domains. The host cell can be a mammalian cell. In addition, U.S. Patent Nos. 5,731,168-A, 5,807,706-A, and 5,821,333-A disclose that there are several techniques for making bispecific antibody fragments, including making bispecific antibody fragments by the use of single chain Fv (scFv) dimmers. However, U.S. Patent Nos. 5,731,168-A, 5,807,706-A, and 5,821,333-

A suggest full length bispecific antibodies, such as those produced by the methods taught therein, may be preferable to bispecific antibody fragments for many clinical applications because of their longer serum half-life and possible effector functions.

In view of the teachings of U.S. Patent Nos. 5,731,168-A, 5,807,706-A, and 5,821,333-A, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have produced a bispecific antibody comprising a first polypeptide comprising a first binding domain and a second polypeptide comprising a second, different binding domain by a process comprising culturing a mammalian host cell containing nucleic acid encoding the polypeptides and recovering the bispecific antibody from the host cell culture. The bispecific antibody so produced would comprise both a first and a second binding domain that comprise a heavy chain domain that interacts with a light chain. The first polypeptide of the bispecific antibody would comprise a multimerization domain that interacts with a multimerization domain of the second polypeptide. The multimerization domains of the first and second polypeptides would comprise an antibody constant domain, namely an antibody constant domain from a C_H3 domain or an IgG. Moreover, the multimerization domains of the first and second polypeptides comprise a free thiol positioned so that a disulfide bond is formed between the first and second polypeptides upon the interaction of the multimerization domains.

One of ordinary skill in the art at the time the invention was made would have been motivated to have done so, because U.S. Patent Nos. 5,731,168-A, 5,807,706-A, and 5,821,333-A suggest full length bispecific antibodies, such as those produced by the methods taught therein, may be preferable to bispecific antibody fragments for many clinical applications and because Mallender, et al teaches that the construction of a model bivalent bispecific molecule provides a foundation for future assembly of similar molecules designed to identify parameters involved in enhanced binding of antibodies due to avidity and dual specificity, which could lead to improving the effectiveness of clinically useful bispecific antibodies.

7. Claims 1, 8, 9, 11, 19, 20, and 30-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vaughan, et al (*Nature Biotechnology* **14**: 309-314, 1996) in view of Bruynck, et al (*British Journal of Cancer* **67**: 436-440, 1993) or Vuillez, et al (*Journal of Nuclear Medicine* **38**: 507-511, 1997) and in view further view of U.S. Patent Nos. 5,731,168-A, 5,807,706-A, and 5,821,333-A.

Vaughan, et al teach human antibody fragments with sub-nanomolar affinities that bind DTPA and CEA and comprise identical variable light chains.

However, Vaughan, et al do not teach a method for preparing a bispecific antibody.

Bruynck, et al teach a method for preparing a bispecific antibody for cancer therapy that comprises binding specificity for the tumor-associated antigen CEA and a radiolabeled chelate, namely DTPA. The host cell of Bruynck, et al, which has nucleic acid encoding the polypeptides of which the bispecific antibody is composed, is a mammalian cell, specifically a transfectoma. The polypeptides of which the bispecific antibody is composed comprise an antibody constant domain, and specifically a C_H3 domain, which forms half the interface at which the polypeptides multimerize.

Vuillez, et al teach a method for preparing and using a bispecific anti-CEA/anti-DTPA antibody. Vuillez, et al teach that the bispecific antibody can be used to improve performances of immunoscintigraphy for cancer staging.

In view of the teachings of the prior art, it would have been *prima facie* obvious to one of ordinary skill in the art to use the high-affinity human antibodies of Vaughan, et to produce a bispecific antibody having on one arm, specificity for CEA, and on the other, specificity for DPTA, because the human antibodies could be used with greater safety and more effectively in humans, as the human antibodies of Vaughan, et al would be even less immunogenic than the chimeric and humanized antibodies of Bruynck, et al.

However, the antibody fragments of Vaughan, et al do not comprise a multimerization domain, such as a constant heavy domain of an immunoglobulin G molecule, which could form the interface at which two antibody fragments having different binding specificity could dimerize to form a bispecific antibody.

U.S. Patent Nos. 5,731,168-A, 5,807,706-A, and 5,821,333-A teach that which set forth in the 35 USC § 103(a) rejection above. The patents teach that the method for producing bispecific antibodies set forth therein provides a mechanism for increasing yields of the heterodimer over other unwanted end-products such as homodimers, which would lack the desired bifunctionality and that it is desirable to increase the yields of the heterodimers over the homomultimers.

In view of the teachings of U.S. Patent Nos. 5,731,168-A, 5,807,706-A, and 5,821,333-A, it would have been *prima facie* obvious to prepare a bispecific antibody according to the methods described therein, which comprises the variable light and variable heavy chains of the human antibody fragments of Vaughan, et al to maximize the yield of a bispecific antibody having on one arm, specificity for CEA, and on the other, specificity for DPTA. One of ordinary skill in the art would have been motivated to have done so because the patents teach that it is desirable to maximize the yield of the bispecific antibody, but moreover because the patents teach that full length bispecific antibodies, such as those produced by the methods taught by the patents, may be preferable to bispecific antibody fragments for many clinical applications, since these antibodies may have effector function.

8. Claims 1, 8, 9, 11, 19, 20, and 30-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vaughan, et al (*Nature Biotechnology* **14**: 309-314, 1996) in view of Reddy, et al (*Anticancer Research* **13**: 2077-2083, 1993) and in view further view of U.S. Patent Nos. 5,731,168-A, 5,807,706-A, and 5,821,333-A.

Vaughan, et al teach human antibody fragments with sub-nanomolar affinities that bind doxorubicin and CEA. The antibody fragments comprise identical variable light chains.

However, Vaughan, et al do not teach a method for preparing a bispecific antibody.

Reddy, et al teach a method for preparing a bispecific antibody for cancer therapy that comprises binding specificity for the tumor-associated antigen CEA and an anticancer agent, namely doxorubicin.

In view of the teachings of the prior art, it would have been *prima facie* obvious to one of ordinary skill in the art to use the high-affinity human antibodies of Vaughan, et to produce a bispecific antibody having on one arm, specificity for CEA, and on the other, specificity for doxorubicin, because a human bispecific antibody could be used with greater safety and more effectively in humans, as the human antibodies of Vaughan, et al would be even less immunogenic than the mouse antibody of Reddy, et al.

However, the antibody fragments of Vaughan, et al do not comprise a multimerization domain, such as a constant heavy domain of an immunoglobulin G molecule, which could form the interface at which two antibody fragments having different binding specificity could dimerize to form a bispecific antibody.

U.S. Patent Nos. 5,731,168-A, 5,807,706-A, and 5,821,333-A teach that which set forth in the 35 USC § 103(a) rejection above. The patents teach that the method for producing bispecific antibodies set forth therein provides a mechanism for increasing yields of the heterodimer over other unwanted end-products such as homodimers, which would lack the desired bifunctionality and that it is desirable to increase the yields of the heterodimers over the homomultimers.

In view of the teachings of U.S. Patent Nos. 5,731,168-A, 5,807,706-A, and 5,821,333-A, it would have been *prima facie* obvious to prepare a bispecific antibody according to the methods described therein, which comprises the variable light and variable heavy chains of the human antibody fragments of Vaughan, et al to maximize the yield of a bispecific antibody having on one arm, specificity for CEA, and on the other, specificity for doxorubicin. One of ordinary skill in the art would have been motivated to have done so because the patents teach that it is desirable to maximize the yield of the bispecific antibody, but moreover because the patents teach that full length bispecific antibodies, such as those produced by the methods taught by the patents, may be preferable to bispecific antibody fragments for many clinical applications, since these antibodies may have effector function.

Conclusion

9. No claims are allowed.

10. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Gulliver, et al (*Journal of Biological Chemistry* **271**: 5338-5356, 1996) teach comparative properties of the single chain antibody and Fv derivatives of mAb 4-4-20.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (703) 305-3008. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony C. Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
March 21, 2003